A STUDY OF LIPID PROFILE IN CHRONIC KIDNEY DISEASE PATIENTS ON CONSERVATIVE MANAGEMENT, HAEMODIALYSIS AND AFTER RENAL TRANSPLANTATION

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CERTIFICATE

This is to certify that the dissertation entitled **"A STUDY OF LIPID PROFILE IN CHRONIC KIDNEY DISEASE PATIENTS ON CONSERVATIVE MANAGEMENT, HAEMODIALYSIS AND AFTER RENAL TRANSPLANTATION"** is the bonafide work of **Dr. K. KARTHICK,** in partial fulfillment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for **M.D General Medicine Branch I** examination to be held in April 2012.

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DECLARATION

I, **Dr. K. KARTHICK,** solemnly declare that, I carried out this dissertation **"A STUDY OF LIPID PROFILE IN CHRONIC KIDNEY DISEASE PATIENTS ON CONSERVATIVE MANAGEMENT, HAEMODIALYSIS AND AFTER RENAL TRANSPLANTATION"** is a bonafide record of work done by me at the Department of General Medicine, Govt. Rajaji Hospital, Madurai, under the guidance of **Dr.G.Bagialakshmi M.D** Associate Professor, Department of General Medicine, Madurai Medical college, Madurai.

This dissertation is submitted to The Tamil Nadu Dr. M. G. R. Medical University, Chennai in partial fulfillment of the rules and regulations for the award of M.D Degree General Medicine Branch-I examination to be held in April 2012.

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CONTENTS

A STUDY OF LIPID PROFILE IN CHRONIC KIDNEY DISEASE PATIENTS ON CONSERVATIVE MANAGEMENT ,ON HAEMODIALYSIS AND AFTER RENAL TRANSPLANTATION

Background:

Chronic kidney disease [CKD] is associated with specific abnormalities in the lipoprotein metabolism both in the early and in the advanced stages of chronic renal failure. Regardless of age, heart disease is a major cause of morbidity and mortality among patients with renal failure. Our study aimed at to estimate lipid profile in CKD patients on conservative management ,on haemodialysis, after renal transplantation and to compare with healthy controls.

Methods :

The study population was 60 patients with 20 patients in each group and 20 healthy controls. Each group had 10 males and 10 females without diabetes or hypertension. After 12 hrs fasting serum lipid profile was estimated in all groups.

Results :

The mean total cholesterol was within optimal level in all the three groups. The mean triglyceride was borderline high in conservative and haemodialysis group ,whereas in post transplant group it was high as per ATP III guidelines. The mean LDL was optimal in conservative and hemodialysis group, high in post transplant group. The mean HDL was decreased in all the three groups. Total cholesterol / HDL ratio was increased in all the three groups.

Conclusion:

From this study it is inferred that dyslipidemia is more common chronic kidney disease patients and more marked in renal transplant recipients.

Keywords:

CKD chronic kidney disease, dyslipidemia, ATP III guidelines , haemodialysis, renal transplantation.

INTRODUCTION

Chronic kidney disease [CKD] is associated with specific abnormalities in the lipoprotein metabolism both in the early and in the advanced stages of chronic renal failure. It has been suggested that the renal dyslipoproteinaemia of renal insufficiency contributes to the progression of glomerular and tubular lesions, with subsequent deterioration of renal function. Regardless of age, heart disease is a major cause of morbidity and mortality among patients with renal failure. Atherosclerotic heart disease is believed to account for approximately 55% of mortality and contributes to a 20-fold increase in ischemic heart disease and to a 10-fold increase in risk of stroke among patients with ESRD (chronic kidney disease stage 5)(8). Hypertension and diabetes mellitus, known risk factors for the development of cardiovascular disease (CVD) in the general population, are also the most common causes for the development of CVD in patients with CKD and ESRD. There are several other important risk factors, such as smoking, proteinuria, oxidative stress, inflammation and dyslipidemia that independently or in combination with elevated blood pressure, can cause deterioration in renal function.

Diabetic CKD patients have higher TG and lower HDL cholesterol than their non-diabetic counterparts, suggesting that diabetes itself exacerbates lipid abnormalities in patients with renal impairment. The

concentration of lipoproteins in renal failure may be increased as a consequence of increased synthesis, decreased catabolism or combination of both. Patients on maintenance haemodialysis also have abnormalties in lipid metabolism like hypertriglyceridaemia and low HDL which could contribute to atherosclerosis and cardiovascular disease. Hyperlipidemia is common after renal transplantation with use of immunosuppressive drugs . There is increasing evidence that post transplant lipoprotein abnormalities may contribute to the development of Cardiovascular disease and shown to increase the risk of chronic rejection, altered graft function. Therefore it is important to screen all patients with CKD for dyslipidemia and treat them as they are considered a very high risk group for CVD.

Since hyperlipidemias become more pronounced as renal failure advances and can be modulated by therapeutic intervention it is worthwhile to study and compare lipid profile abnormalities in renal failure patients on different modes of management.

A prospective study was taken up, to study the lipid profile in patients of chronic renal failure

a. on conservative management

b. on regular haemodialysis

c. after renal transplantation and to compare with healthy controls

AIM OF THE STUDY

1. To estimate the levels of
    - Serum triglycerides,
    - Serum total cholesterol,
    - High density lipoprotein cholesterol,
    - Low density lipoprotein cholesterol,
    - Ratio of total cholesterol to HDL cholesterol level in patients of chronic kidney disease,

    a. On conservative management

    b. On regular haemodialysis

    c. Following renal transplantation

2. To compare the lipid profile of the above mentioned patients with that of healthy controls.
3. The principal reason to evaluate dyslipidemia patients with CKD is to detect abnormalities that may be treated to reduce the incidence of ACVD.(Atherosclerotic cardiovascular disease)

REVIEW OF LITERATURE

LIPOPROTEINS

Lipoproteins are complexes of lipids and proteins that are essential for the transport of cholesterol, triglycerides, and fat-soluble vitamins.

Lipoprotein Classification and Composition

Lipoproteins play an essential role in the absorption of dietary cholesterol, long-chain fatty acids, and fat-soluble vitamins; the transport of triglycerides, cholesterol, and fat-soluble vitamins from the liver to peripheral tissues; and the transport of cholesterol from peripheral tissues to the liver.

Lipoproteins contain a core of hydrophobic lipids (triglycerides and cholesteryl esters) surrounded by hydrophilic lipids (phospholipids, unesterified cholesterol) and proteins that interact with body fluids. The plasma lipoproteins are divided into five major classes based on their relative density :

1. Chylomicrons,
2. Very low-density lipoproteins (VLDLs),
3. Intermediate-density lipoproteins (IDLs),
4. Low-density lipoproteins (LDLs), and
5. High-density lipoproteins (HDLs).

Each lipoprotein class comprises a family of particles that vary slightly in density, size and protein composition. The density of a lipoprotein is determined by the amount of lipid per particle. HDL is the smallest and most dense lipoprotein, whereas chylomicrons and VLDLs are the largest and least dense lipoprotein particles. Most plasma triglyceride is transported in chylomicrons or VLDLs, and most plasma cholesterol is carried as cholesteryl esters in LDLs and HDLs.

CHYLOMICRONS AND VERY LOW DENSITY LIPOPROTEINS

By definition, chylomicrons are found in chyle formed only by the lymphatic system draining the intestine. They are responsible for the transport of all dietary lipids into the circulation. Small quantities of VLDL are also to be found in chyle; however, most of the plasma VLDL are of hepatic origin. They are the vehicles of transport of triacylglycerol from the liver to the extrahepatic tissues.

There are striking similarities in the mechanisms of formation of chylomicrons by intestinal cells and of VLDL by hepatic parenchymal cells perhaps because apart from the mammary gland the intestine and liver are the only tissues from which particulate lipid is secreted. Newly secreted or "nascent" chylomicrons and VLDL contain only a small amount of apolipoproteins C and E, and the full complement is acquired from HDL in the circulation. Apo B is essential for chylomicron and VLDL formation.

Triacylglycerols of Chylomicrons & VLDL are hydrolyzed by Lipoprotein Lipase. Both phospholipids and apo C-II are required as cofactors for lipoprotein lipase activity, while apo A-II and apo C-III act as inhibitors. Hydrolysis takes place while the lipoproteins are attached to the enzyme on the endothelium. Triacylglycerol is hydrolyzed progressively through a diacylglycerol to a monoacylglycerol that is finally hydrolyzed to free fatty acid plus glycerol. Fatty acids originating from chylomicron triacylglycerol are delivered mainly to adipose tissue, heart, and muscle (80%), while about 20% goes to the liver. Reaction with lipoprotein lipase results in the loss of approximately 90% of the triacylglycerol of chylomicrons and in the loss of apo C (which returns to HDL)but not apo E, which is retained. The resulting chylomicron remnant is about half the diameter of the parent chylomicron and is relatively enriched in cholesterol and cholesteryl esters because of the loss of triacylglycerol . Similar changes occur to VLDL, with the formation of VLDL remnants or IDL (intermediate-density lipoprotein).

Chylomicron remnants are taken up by the liver by receptor mediated endocytosis, and the cholesteryl esters and triacylglycerols are hydrolyzed and metabolized. Uptake is mediated by a receptor specific for apo E and both the LDL (apo B-100,apo E) receptor and the LRP (LDL receptor-related protein) are believed to take part.

LOW DENSITY LIPOPROTEINS

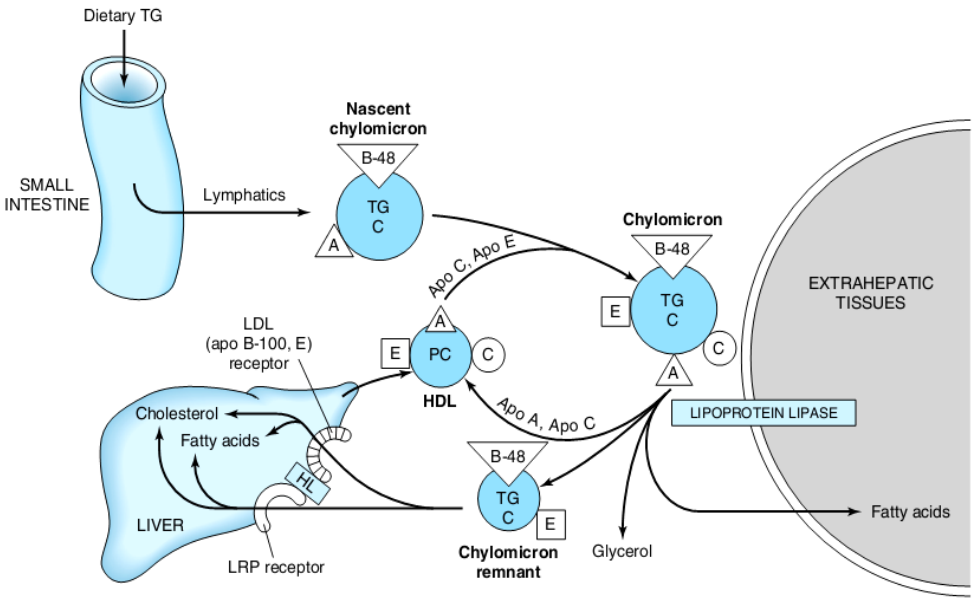
VLDL is the precursor of IDL, which is then converted to LDL. Only one molecule of apo B-100 is present in each of these lipoprotein particles, and this is conserved during the transformations. Thus, each LDL particle is derived from only one VLDL particle. Two possible fates await IDL. It can be taken up by the liver directly via the LDL (apo B-100, E) receptor, or it is converted to LDL. In humans, a relatively large proportion forms LDL, accounting for the increased concentrations of LDL in humans compared with many other mammals. The liver and many extrahepatic tissues express the LDL (B-100, E) receptor. It is so designated because it is specific for apo B-100 but not B-48, which lacks the carboxyl terminal domain of B-100 containing the LDL receptor ligand, and it also takes up lipoproteins rich in apo E. This receptor is defective in familial hypercholesterolemia. Approximately 30% of LDL is degraded in extrahepatic tissues and 70% in the liver. A positive correlation exists between the incidence of coronary atherosclerosis and the plasma concentration of LDL cholesterol.

HIGH DENSITY LIPOPROTEIN

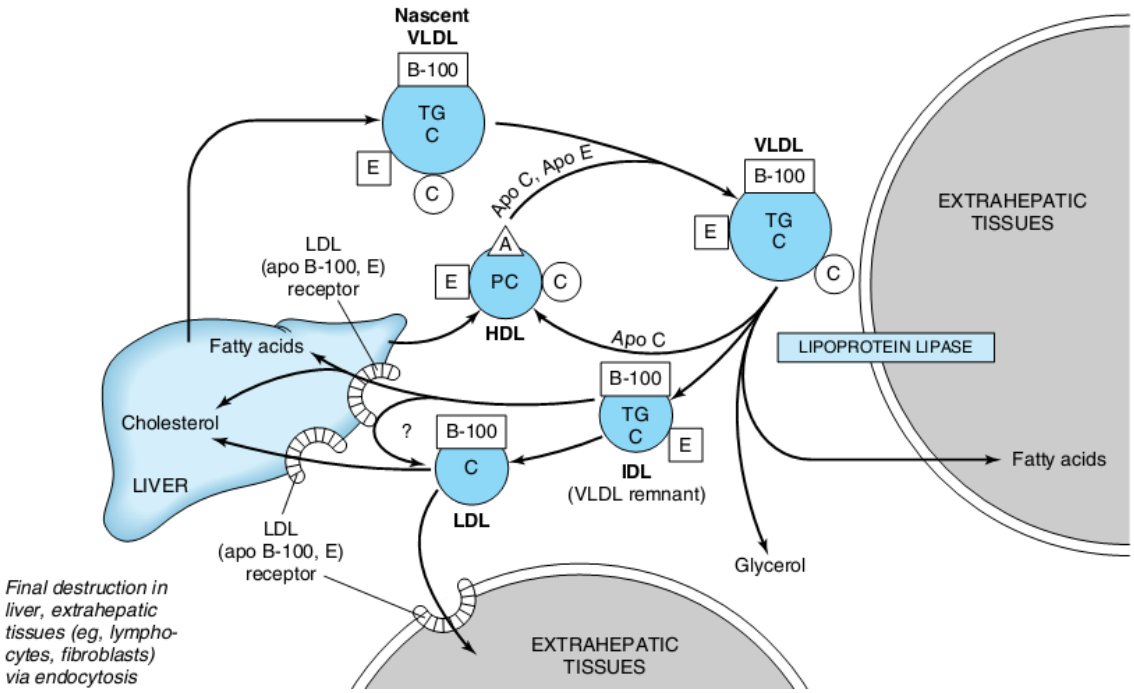
HDL is synthesized and secreted from both liver and intestine . However, apo C and apo E are synthesized in the liver and transferred from liver HDL to intestinal HDL when the latter enters the plasma. A major

function of HDL is to act as a repository for the apo C and apo E required in the metabolism of chylomicrons and VLDL. Nascent HDL consists of discoid phospholipid bilayers containing apo A and free cholesterol. LCAT and the LCAT activator apo A-I bind to the disk, and the surface phospholipid and free cholesterol are converted into cholesteryl esters and lysolecithin. The nonpolar cholesteryl esters move into the hydrophobic interior of the bilayer, whereas lysolecithin is transferred to plasma albumin. Thus, a nonpolar core is generated, forming a spherical, pseudomicellar HDL covered by a surface film of polar lipids and apolipoproteins. In this way, the LCAT system is involved in the removal of excess unesterified cholesterol from lipoproteins and tissues. The class B scavenger receptor B1 (SR-B1) has recently been identified as an HDL receptor in the liver and in steroidogenic tissues. HDL binds to the receptor via apo A-I and cholesteryl ester is selectively delivered to the cells, but the particle itself, including apo A-I, is not taken up. The transport of cholesterol from the tissues to the liver is known as reverse cholesterol transport and is mediated by a HDL cycle . The smaller HDL3 accepts cholesterol from the tissues via the ATP-binding cassette transporter-1 (ABC-1). ABC-1 is a member of a family of transporter proteins that couple the hydrolysis of ATP to the binding of a substrate, enabling it to be transported across the membrane. After being accepted by HDL3, the cholesterol is then esterified by LCAT, increasing

the size of the particles to form the less dense HDL2. The cycle is completed by the re-formation of HDL3, either after selective delivery of cholesteryl ester to the liver via the SR-B1 or by hydrolysis of HDL2 phospholipid and triacylglycerol by hepatic lipase. In addition, free apo A-I is released by these processes and forms pre-HDL after associating with a minimum amount of phospholipid and cholesterol. Preβ-HDL is the most potent form of HDL in inducing cholesterol efflux from the tissues to form discoidal HDL. Surplus apo A-I is destroyed in the kidney.



Metabolic fate of chylomicrons.(2)



Metabolic fate of very low density lipoproteins (VLDL) and production of low-densit lipoproteins (LDL).(2)

APOLIPOPROTEIN

The protein moiety of a lipoprotein is known as an apo-lipoprotein or apoprotein, constituting nearly 70% of some HDL and as little as 1% of chylomicrons. Some apolipoproteins are integral and cannot be removed, whereas others are free to transfer to other lipoproteins.

One or more apolipoproteins (proteins or polypeptides) are present in each lipoprotein. The major apolipoproteins of HDL (α-lipoprotein) are designated A. The main apolipoprotein of LDL (β-lipoprotein) is

apolipoprotein B (B-100) and is found also in VLDL. Chylomicrons contain a truncated form of apoB (B-48) that is synthesized in the intestine, while B-100 is synthesized in the liver. Apo B-100 is one of the longest single polypeptide chains known, having4536 amino acids and a molecular mass of 550,000 Da. Apo B-48 (48% of B-100) is formed from the same mRNA as apo B-100 after the introduction of a stop signal by an RNA editing enzyme. Apo C-I, C-II, and C-III are smaller polypeptides (molecular mass 7000–9000 Da) freely transferable between several different lipoproteins. Apo E is found in VLDL, HDL, chylomicrons, and chylomicron remnants; it accounts for 5–10% of total VLDL apolipoproteins in normal subjects.

Apolipoproteins carry out several roles:

(1) they can form part of the structure of the lipoprotein, eg, apo B;

(2) they are enzyme cofactors, eg, C-II for lipoprotein lipase, A-I for lecithin:cholesterol acyltransferase, or enzyme inhibitors, eg, apo A-II and apo C-III for lipoprotein lipase, apo C-I for cholesteryl ester transfer protein;

(3) they act as ligands for interaction with lipoprotein receptors in tissues, eg, apo B-100 and apo E for the LDL receptor, apo E for the LDL receptor-related protein (LRP), which has been identified as the remnant receptor, and apo A-I for the HDL receptor. The functions of apo A-IV and apo D, however, are not yet clearly defined.

SUMMARY OF LIPOPROTEIN METABOLISM

Lipids are derived from food (exogenous) or are synthesised in the body **(endogenous).**

Transport of Dietary Lipids (Exogenous Pathway)

The exogenous pathway of lipoprotein metabolism permits efficient transport of dietary lipids. Dietary triglycerides are hydrolyzed by lipases within the intestinal lumen and emulsified with bile acids to form micelles. Dietary cholesterol, fatty acids, and fat-soluble vitamins are absorbed in the proximal small intestine. Cholesterol and retinol are esterified (by the addition of a fatty acid) in the enterocyte to form cholesteryl esters and retinyl esters, respectively. Longer-chain fatty acids (>12 carbons) are incorporated into triglycerides and packaged with apoB-48, cholesteryl esters, retinyl esters, phospholipids, and cholesterol to form chylomicrons. Nascent chylomicrons are secreted into the intestinal lymph and delivered via the thoracic duct directly to the systemic circulation, where they are extensively processed by peripheral tissues before reaching the liver. The particles encounter lipoprotein lipase (LPL), which is anchored to a glycosylphosphatidylinositol-anchored protein, (GPIHBP1), that is attached to the endothelial surfaces of capillaries in adipose tissue, heart, and skeletal muscle . The triglycerides of chylomicrons are hydrolyzed by LPL, and free fatty acids are released. ApoC-II, which is transferred to circulating

chylomicrons from HDL, acts as a required cofactor for LPL in this reaction. The released free fatty acids are taken up by adjacent myocytes or adipocytes and either oxidized to generate energy or reesterified and stored as triglyceride. Some of the released free fatty acids bind to albumin before entering cells and are transported to other tissues, especially the liver. The chylomicron particle progressively shrinks in size as the hydrophobic core is hydrolyzed and the hydrophilic lipids (cholesterol and phospholipids) and apolipoproteins on the particle surface are transferred to HDL, creating chylomicron remnants. Chylomicron remnants are rapidly removed from the circulation by the liver through a process that requires apoE as a ligand for receptors in the liver. Consequently, few, if any, chylomicrons or chylomicron remnants are present in the blood after a 12-hour fast, except in patients with disorders of chylomicron metabolism.

Transport of Hepatic Lipids (Endogenous Pathway)

The endogenous pathway of lipoprotein metabolism refers to the secretion of apoB-containing lipoproteins from the liver and the metabolism of these triglyceride-rich particles in peripheral tissues . VLDL particles resemble chylomicrons in protein composition but contain apoB-100 rather than apoB-48 and have a higher ratio of cholesterol to triglyceride . The triglycerides of VLDL are derived predominantly from the esterification of long-chain fatty acids in the liver. The packaging of hepatic triglycerides

with the other major components of the nascent VLDL particle (apoB-100, cholesteryl esters, phospholipids, and vitamin E) requires the action of the enzyme microsomal triglyceride transfer protein (MTP). After secretion into the plasma, VLDL acquires multiple copies of apoE and apolipoproteins of the C series by transfer from HDL. As with chylomicrons, the triglycerides of VLDL are hydrolyzed by LPL, especially in muscle, heart, and adipose tissue. After the VLDL remnants dissociate from LPL, they are referred to as IDLs, which contain roughly similar amounts of cholesterol and triglyceride. The liver removes approximately 40–60% of IDL by LDL receptor–mediated endocytosis via binding to apoE. The remainder of IDL is remodeled by hepatic lipase (HL) to form LDL. During this process, most of the triglyceride in the particle hydrolyzed, and all apolipoproteins except apoB-100 are transferred to other lipoproteins. The cholesterol in LDL accounts for more than one-half of the plasma cholesterol in most individuals. Approximately 70% of circulating LDL is cleared by LDL receptor–mediated endocytosis in the liver. *Lipoprotein(a)* [Lp(a)] is a lipoprotein similar to LDL in lipid and protein composition, but it contains an additional protein called *apolipoprotein(a)* [apo(a)]. Apo(a) is synthesized in the liver and attached to apoB-100 by a disulfide linkage. The major site of clearance of Lp(a) is the liver, but the uptake pathway is not known.

CHRONIC KIDNEY DISEASE(CKD)

CKD is defined according to the presence ,for atleast 3 months ,of either of the following :

1. Structural or functional abnormalities of the kidney that can lead to kidney failure
2. GFR <60 ml /min/1.73m^2

STAGES OF CKD

The definitions of Stages 1–5 CKD are based on measured or estimated GFR , where the GFR is estimated from the serum creatinine using an established formula, as described in the KDOQI CKD Guidelines.

Stage 1 CKD is defined by estimated GFR ≥90 mL/ min/1.73 m^2, with evidence of kidney damage (as defined above).

Stage 2 CKD is defined as evidence of kidney damage with mildly decreased GFR of 60–89 mL/min/1.73 m^2.

Stage 3 CKD: The level of estimated GFR is 30-59 Ml/min/1.73 m^2.

Stage 4 CKD : The level of estimated GFR is 15 -29 mL/min/1.73 m^2 .

Stage 5 CKD is defined as GFR <15 mL/min/1.73 m^2, or the clinical indication for kidney replacement therapy with maintenance hemodialysis, peritoneal dialysis, or transplantation.

Dyslipidemia Associated with Chronic Kidney Disease

CKD is characterized by specific metabolic abnormalities of plasma lipoproteins . These abnormalities involve all lipoprotein classes and shows variations depending on the degree of renal impairment, the etiology of primary disease, the presence of nephrotic syndrome (NS) and the method of dialysis [hemodialysis (HD) or peritoneal dialysis (PD)] for patients undergoing renal replacement therapy. In patients with CKD, uremia related, non -traditional risk factors, such as, inflammation, oxidative stress, anemia, malnutrition, vascular calcification (due to alterations in calcium and phosphorus metabolism) and endothelial dysfunction have been proposed to play a central role.

PROTEINURIA

Hyperlipidemia of the nephrotic syndrome is clinically obvious. There is growing evidence that non-nephrotic proteinuria also affects the physiology of lipoproteins. Several studies have shown an association between microalbuminuria and dyslipidemia, as well as with other components of metabolic syndrome. In fact, patients with diabetes mellitus or hypertension with macroalbuminuria or microalbuminuria have a higher rate of dyslipidemia than those with normoalbuminuria. Since CKD is often associated with non-nephrotic proteinuria, this could be a mediator of uremic dyslipidemia.

ALTERATIONS OF TRIGLYCERIDE - RICH LIPOPROTEIN METABOLISM IN CKD

Hypertriglyceridemia is one of the most common quantitative lipid abnormalities in patients with CKD [10,11]. The concentrations of triglyceride-rich lipoproteins [very low density lipoprotein (VLDL), chylomicrons, and their remnants] start to increase in early stages of CKD and show the highest values in NS and in dialysis patients, especially those who are treated with PD.

Several studies have shown that patients with impaired renal function exhibit increased concentrations of triglycerides even though serum creatinine levels are within normal limits [12,13] . Also, individuals with CKD usually display abnormal increases in serum triglyceride levels after a fat meal (postprandial lipemia). The predominant mechanism responsible for increased concentration of triglyceride-rich lipoproteins in predialysis patients is one of delayed catabolism. The reduced catabolic rate is likely due to diminished lipoprotein lipase activity as a consequence of the downregulation of the enzyme gene and the presence of lipase inhibitors . Apolipoprotein C-III is a potent inhibitor of lipoprotein lipase whereas apolipoprotein C-II is an activator of the same enzyme. A decrease in apolipo-protein C-II/C-III ratio due to adisproportionate increase in plasma apolipoprotein C-III is a possible cause of lipoprotein lipase inactivation in

uremia [14,15]. It was also suggested that secondary hyperparathyroidism is involved in the impaired catabolism of triglyceride-rich lipoproteins, provided an additional mechanism by which CKD may raise plasma triglyceride concentration. Except of the low catabolic rate, the increased hepatic production of triglyceride-rich lipoproteins may also play a contributory role in the pathogenesis of dyslipidemia in renal disease. It is well known that CKD causes insulin resistance which can, in turn, promote hepatic VLDL production. Thus, it could be hypothesized that the insulin resistance driven overproduction of VLDL may significantly contribute to the development of hypertiglyceridemia in patients with CKD.[16]

ALTERATIONS IN LOW DENSITY LIPOPROTEIN (LDL) METABOLISM IN CKD

Chronic kidney disease in the absence of heavy proteinuria does not significantly affect gene expressions of either hydroxyl-3-methylglutaryl-CoA reductase (HMG-CoA reductase) which is the rate-limiting enzyme for cholesterol biosynthesis, or that of cholesterol 7a-hydroxylase which is the rate-limiting enzyme for cholesterol catabolism and conversion to bile acids . Also, LDL receptor-mediated cholesterol uptake plays an important role in cholesterol homeostasis. CKD in the absence of heavy proteinuria or significant glomerulosclerosis does not alter hepatic LDL receptor gene expression [17].

Chronic kidney disease patients, with or without heavy proteinuria, display important qualitative alterations in LDL metabolism. The proportion of small dense LDL particles, which is considered to be highly atherogenic, is increased [18,19]. Small dense LDL is a subtype of LDL that has high propensity to penetrate the vessel wall, becomes oxidized and triggers the atherosclerotic process.

HIGH DENSITY LIPOPROTEIN (HDL) AND CKD

Patients with CKD have, generally, reduced plasma HDL-cholesterol levels compared to individuals with normal renal function [10,20]. This can be attributed to several mechanisms. Thus, patients with impaired renal function usually exhibit decreased levels of apolipoproteins AI and AII (the main protein constituents of HDL) , diminished activity of LCAT (the enzyme responsible for the esterification of free cholesterol in HDL particles) [21,22], as well as increased activity of cholesteryl ester transfer protein (CETP) that facilitates the transfer of cholesterol esters from HDL to triglyceride-rich lipoproteins thus reducing the serum concentrations of HDL-cholesterol. In addition to their reduced efficiency as cholesterol acceptors, HDL particles from individuals with impaired renal function have less effective antioxidative and anti-inflammatory function. This impairment can, at least in part, be attributed to the reduction in the activities of HDL-associated enzymes, such as paraoxonase (an enzyme that inhibits the LDL oxidation).[23]

LIPOPROTEIN (a) (LP(a)) AND CKD

Lp(a) is a lipoprotein similar to LDL in lipid and protein composition, but additionally contains apo(a), which is synthesized in the liver and is linked to apo-B-100 by a disulfide bridge. This lipoprotein has high homology with plasminogen, interfering with fibrinolysis, and also binds to macrophages, promoting the formation of foam cells. Plasma concentrations of Lp(a) are strongly genetically determined by the apo(a) gene. Individuals with apo(a) isoforms of high molecular weight usually have low mean Lp(a) concentrations, whereas those with isoforms of low molecular weight usually exhibit more elevated plasma concentrations of Lp(a).[24,25]

In addition to the genetic influence, Lp(a) concentrations are also affected by the GFR in renal disease. These concentrations are increased in CKD and in nephritic syndrome. In the first case, this increase appears to result from decreased catabolism, while in the second, it results from increased synthesis.

Summary of lipoprotein profile abnormality

1. Increase in Total Triglycerides.
2. Increase in VLDL and LDL, HDL triglycerides
3. Slight increase of total cholesterol.
4. Decrease in HDL Cholesterol

Summary of apolipoprotein profile abnormality

1. Decreased Apo A-I, Apo A-II
2. Increased Apo C-III
3. Decreased Apo –E
4. Normal or increased levels of Apo B

ALTERATIONS OF TRIGLYCERIDE-RICH LIPO-PROTEIN METABOLISM IN DIALYSIS PATIENTS WITH CKD

The initiation of renal replacement therapy, as well as the choice of dialysis modality, may also influence the levels of triglyceride-rich lipoproteins in ESRD patients [11]. The pathophysiological mechanisms responsible for these alterations seem to be generally similar with those described in predialysis patients with CKD. However, factors related to the procedure of renal replacement therapy seem to contribute to the increased levels of triglycerides observed in this patient group. In HD patients the repeated use of low-molecular heparins for anticoagulation may lead to a defective catabolism of triglyceride-rich lipoproteins as heparin releases lipoprotein lipase from the endothelia surface and thus its chronic use may result in lipoprotein lipase depletion.

In addition, controversy exists as to whether low-molecular weight heparins have a more favourable effect on the lipid profile of HD patients compared to standard unfractionated heparin [26, 27]. Also, studies on the influence of the type of membrane used in HD yielded conflicting results. It has been shown that the use of high-flux polysulfone or cellulose triacetate membranes is accompanied by a significant reduction in serum triglyceride. This improvement could, at least in part, be attributed to an increase in the apolipoprotein C-II/CIII ratio which increases the activity of lipoprotein lipase and facilitates the intravascular lipolysis of triglyceride-rich lipoproteins [28].

ALTERATIONS IN LOW DENSITY LIPOPROTEIN (LDL) METABOLISM IN DIALYSIS PATIENTS WITH CKD

In HD patients the serum lipid concentrations resemble those of predialysis patients with CKD, which means that total and LDL cholesterol levels are generally normal, whereas the subfractionation of apolipoprotein B-containing lipoproteins usually reveals a predominance of small dense particles [29]. On the other hand, CAPD patients exhibit a more atherogenic lipid profile that is characterized by higher total and LDL cholesterol values and increased concentrations of small dense LDL and apolipoprotein B [11]. A number of possible factors associated with the PD treatment may explain those alterations in lipoprotein metabolism. It is known that CAPD

(continuous ambulatory peritoneal dialysis) patients lose substantial amounts of plasma proteins into the peritoneal dialysate. This protein loss may, in turn, stimulate the hepatic synthesis of albumin and other liver-derived proteins, including cholesterol enriched lipoproteins [30]. It should be also mentioned that, in CAPD patients, substantial amounts of apolipoproteins and intact lipoproteins are lost via the peritoneal cavity. However the pathophysiological significance of these loses remains unclear.

HIGH DENSITY LIPOPROTEIN (HDL) METABOLISM IN DIALYSIS PATIENTS WITH CKD

Hemodialysis procedure may also have a contributory role in the reduced HDL cholesterol levels of dialysis patients. Thus, in dialysis patients the type of membrane and dialysate used in HD procedure may influence the HDL-cholesterol levels. It has been shown that the use of high-flux instead of low flux membranes is associated with an increase in apolipoprotein AI and HDL-cholesterol values. [31,32]. In addition, the type of dialysate may also significantly affect the serum levels of lipoproteins in HD patients. Indeed, it has been shown that the use of bicarbonate dialysate may result in higher HDL-cholesterol concentrations than the use of acetate dialysate [33].

LIPID PROFILE CHANGES IN DIFFERENT GROUPS:(4)

Table 1 Lipid profile in patients with chronic renal insufficiency undergoing dialysis or with nephrotic syndrome.[1,4]

	CRI	Nephrotic syndrome	Hemodialysis	Peritoneal dialysis
Total cholesterol	↔	↑↑	↔, ↓	↑, ↔
LDL cholesterol	↔	↑↑	↔, ↓	↑, ↔
HDL cholesterol	↓	↓	↓	↓
Non-HDL cholesterol	↑	↑↑	↔, ↓, ↑	↑
Triglycerides	↑	↑↑	↑	↑
Lp(a)	↑	↑↑	↑	↑↑

Normal (↔), increased (↑), markedly increased (↑↑), and decreased (↓) plasma levels compared with non-uremic individuals.
LDL: low density lipoproteins; HDL: high density lipoproteins; Lp(a): lipoprotein (a); CRI: chronic renal insufficiency.

HYPERLIPIDEMIA AFTER KIDNEY TRANSPLANTATION

Hyperlipidemia is common after renal transplantation. The pathogenesis of hyperlipidemia in renal transplant patients is poorly understood. Several possible causes include immunosuppressive therapy, genetic predisposition, age, gender, body-weight gain, renal function, proteinuria, diabetes, and antihypertensive drugs. However, the relative contribution of these factors in the genesis of post-transplant hyperlipidemia is unclear. Post-transplant hyperlipidemia is related to immunosuppressive therapy in a dose-dependent fashion [34]. Moreover, the association between immunosuppressive therapy and hyperlipidemia has

generally been observed early after transplantation, and it is probable that the persistent lipid abnormalities in the late post-transplant period are also the result of factors other than immunosuppressive therapy.

After trans-plantation and renal function recovery, lipid disturbances usually persist but show a different profile due to the various effects of immunosuppressive drugs, such as calcineurin inhibitors (cyclosporine and tacrolimus), antiproliferative drugs (mycophenolate mofetil and azathioprine), mammalian target of rapamycin inhibitors (sirolimus and everolimus), and corticosteroids[36,37]. The most frequent alterations in the lipid profile of renal transplant recipients are elevated total cholesterol, LDL cholesterol and trigly-ceride concentrations, and decreased HDL cholesterol concentrations, although an increase in HDL cholesterol is frequently observed in patients treated with corticosteroids, such as prednisone and deflazacort.

Post-Transplant Triglyceride-Rich Lipoprotein Metabolism

The altered metabolism of triglyceride-rich lipoproteins is probably the result of either increased hepatic secretion of very-low-density lipoproteins (VLDL), or decreased peripheral triglyceride-rich lipoprotein removal, or both [35]. Cattran et al. Studied triglyceride turnover sequentially for up to 3 years post-transplantation and demonstrated that overproduction of triglycerides was the predominant defect.

Hyperinsulinemia secondary to insulin-resistance might stimulate hepatic triglyceride-rich lipoprotein production. Indeed, hyperinsulinemia has been positively, but inconsistently, correlated to triglyceride concentrations in renal transplant patients. Corticosteroid treatment is probably the primary cause of insulin-resistance (36). Corticosteroids could increase the rate-limiting enzymes of lipogenesis, acetyl-C0A carboxylase, and free fatty acid synthetase.

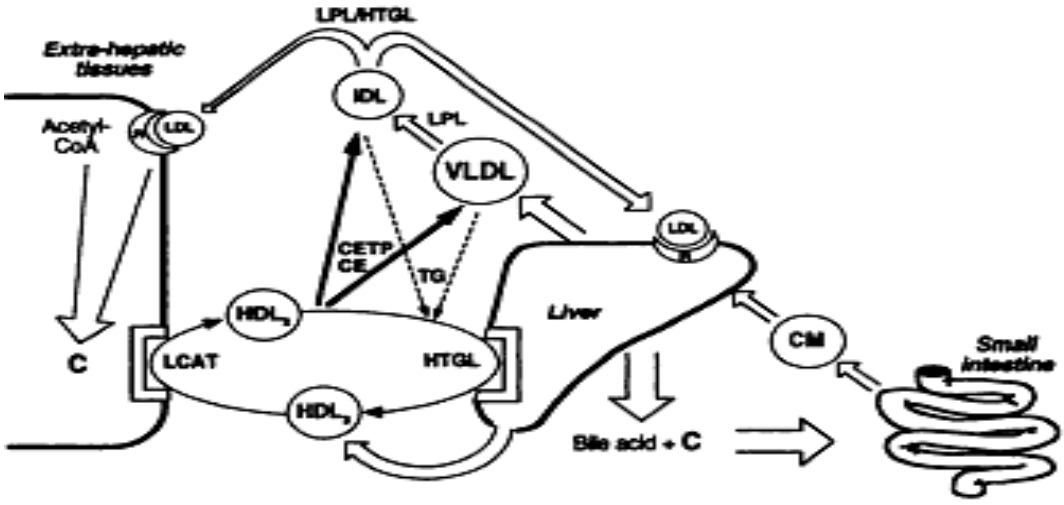
A decrease in the catabolism of triglyceride-rich lipoproteins in renal transplant patients is evidenced by a decrease in VLDL turnover rate, a decrease in the fractional clearance rate of intra lipid , and a decrease in the postprandial triglyceride clearance rate . Lipoprotein lipase (LPL) and hepatic triglyceride lipase (HTGL) are responsible for the catabolism of triglyceride-rich lipoproteins. The function of LPL and HTGL, measured by total post-heparin lipolytic activity, have been reported to be normal or reduced. [37,38]

Post-Transplant Cholesterol-Rich Lipoprotein Metabolism

Increased synthesis of VLDL with normal conversion of VLDL to LDL could cause increased levels of LDL [39]. However, whether the conversion of VLDL to LDL is normal in renal transplantation is unclear. Triglyceride enrichment of LDL has been documented in corticosteroid treated patients, and triglyceride-enriched LDL may be less accessible for

receptor uptake and degradation . As previously mentioned, corticosteroids and cyclosporine could theoretically interfere with LDL-receptor activity [40,41]. Moreover, the decrease of bile-acid synthesis caused by cyclosporine, as demonstrated In vitro, could cause downregulation of hepatic LDL-receptor expression by feedback mechanisms[42,43]. It should be noted that renal transplant patients have several factors (including insulin resistance, renal failure, decreased apo C-Il/C-Ill ratio, and beta-blocker use) that could theoretically reduce the synthesis and/or the activity of these lipases. Moreover, the abnormal lipid and apoprotein content of triglyceride-rich lipoproteins could theoretically inhibit their catabolism, and triglyceride enrichment of VLDL has been documented in renal transplant patients [40,41] . Finally, because the LDL receptor also recognizes VLDL, reduced hepatic LDL-receptor number and/or function could lead to the accumulation of triglyceride-rich lipoproteins. Corticosteroids have been shown to inhibit LDL-receptor activity . Cyclosporine could theoretically interfere with LDL receptors, leading to increased LDL levels. [44,45,46]

Schematic representation of triglycerides and cholesterol metabolism.[6]



Effect of immunosuppressive drugs on lipid profile[4] :

Table 2 Effect of immunosuppressive drugs on lipid parameters.[16]

	Total cholesterol	LDL cholesterol	HDL cholesterol	Triglycerides
Cyclosporine	↑↑	↑↑	↓	↑↑
Tacrolimus	↑	↑	↓	↑
Sirolimus	↑↑	↑↑	↓	↑↑↑
Everolimus	↑↑	↑↑	↓	↑↑↑
Mycophenolate mofetil	–	–	–	–
Azathioprine	–	–	–	–
Prednisone	↑	↑	↑	↑
Deflazacort	↑	↑	↑↑	↑

Normal (↔), increased (↑), markedly increased (↑↑), and decreased (↓) plasma levels.
LDL: low density lipoproteins; HDL: high density lipoproteins.

Summary of Lipid Profile Changes after Transplantation

1. Increase in total cholesterol with increase in VLDL, and LDL cholesterol.
2. Increase in Triglycerides.
3. Decrease in HDL cholesterol

DYSLIPIDEMIA IN INDIANS

Table : 3

Optimum level of Risk factors for Asian Indians:

Risk factors	Male	Female
Cholesterol (mg/dl)	<150	<150
LDL(mg/dl)	<100	<100
HDL (mg/dl)	>40	>50
Triglyceride (mg/dl)	<150	<150
Lp(a) (mg/dl)	<20	<20

TREATMENT OF ADULTS WITH DYSLIPIDEMIAS

GUIDELINE 4

► For adults with Stage 5 CKD and fasting triglycerides >500 mg/dL (>5.65 mmol/L) that cannot be corrected by removing an underlying cause, treatment with therapeutic lifestyle changes (TLC) and a triglyceride lowering agent should be considered.

- For adults with Stage 5 CKD and LDL >100 mg/dL (>2.59 mmol/L), treatment should be considered to reduce LDL to <100 mg/dL (<2.59 mmol/L).
- For adults with Stage 5 CKD and LDL <100 mg/dL (<2.59 mmol/L), fasting triglycerides >200 mg/dL (>2.26 mmol/L), and non-HDL cholesterol (total cholesterol minus HDL) >130 mg/dL (>3.36 mmol/L), treatment should be considered to reduce non-HDL cholesterol to <130mg/dL (<3.36 mmol/L).

Table : 4
The Management of Dyslipidemias in Adults with Chronic Kidney disease

Dyslipidemia	Goal	Initiate	Increase	Alternative
TG> 500mg/dl	TG <500mg/dl	TLC	TLC + Fibrate or Niacin	Fibrate or Niacin
LDL **100 – 129mg/dl**	LDL < 100mg/dl	TLC	TLC + low dose Statin	Bile acid seq or Niacin
LDL **> 130 mg/dl**	LDL < 100mg/dl	TLC + low dose Statin	TLC + max dose Statin	Bile acid seq or Niacin
TG 200mg/dl and non HDL >130mg/dl	non HDL <130mg/dl	TLC + low dose Statin	TLC + max dose Statin	Fibrate or Niacin

TLC – Therapeutic Lifestyle Changes.

Therapeutic Lifestyle Changes (TLC) for Adults with Chronic Kidney Disease.

Diet

Emphasize reduced saturated fat:

Saturated fat : <7% of total calories

Polyunsaturated fat : up to 10% of total calories

Monounsaturated fat : up to 20% of total calories

Total fat : 25 %- 35% of total calories

Cholestrol : <200 mg per day

Carbohydrates : 50%-60% of total calories

Emphasize components that reduce dyslipidemia:

Fiber 20 -30 g /day emphasize 5 -10g/day viscous (soluble) fiber.

Consider plant stanols / sterols 2g/day

Improve glycemic control

Emphasize total calories to attain /maintain standard NHANES body weight

Match intake of overall energy (calories) to overall energy needs

Body Mass Index 25 -28kg/m2

Waist circumference

Men <40 inches (102cm)

Women <35 inches (102cm)

Waist – hip Ratio (Men <1.0; Women <0.8).

ROLE OF STATINS

Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase and are the most widely studied drug class in the treatment of dyslipidemia in ESRD[47]. The renoprotective effect of statins may not be only due to lipid reduction, but also to a decrease of renal interstitial inflammation, improvement of renal hemodynamics, and a decrease in glomerular proteinuria. Statins may also have a beneficial effect on vascular stiffness and endothelial function in renal failure. Current recommendations are to reduce the statin dose by 50% in dialysis patients, except for atorvastatin and pravastatin[48]. In transplant recipients, a lower starting dose of statins should be used, particularly with concomitant use of cyclosporine.

Nicotinic acid

Nicotinic acid is highly effective in increasing HDL by decreasing cholesterol transfer from HDL to VLDL and also by decreasing HDL clearance and is the only available drug to substantially lower plasma Lp(a). This drug also reduces VLDL secretion by the liver. In the general population nicotinic acid has been shown to improve cardiac and cerebrovascular prognosis. Studies in CKD are small and of short duration, but showed the expected changes in lipid profile.

Fibrates

Fibrates are PPAR a activators. Activation of this transcriptional factor increases oxidation of fatty acids in the liver, kidney, heart, and skeletal muscle and reduces hepatic production of apo-CIII and increases expression of LPL, apo-AI, and apo-AII, as well as increases HDL and lowers total cholesterol, triglycerides, and LDL. Given the early development of hypertriglyceridemia in CKD, fibrates would be logical candidates for the treatment of dyslipidemia in this disease, but are not often used because of the risk of rhabdomyolysis,[49] worsening of renal function, impairment of liver function, and elevation of homocysteine in these patients. The NKF guidelines favour the use of gemfibrozil because this drug does not requires dose adjustment for the decrease in GFR and its pharmacokinetics are not altered in this context. These guidelines discourage the use of fibrates in patients with GFR< 15 mL/min.[24]

Ezetimibe

Ezetimibe has low interaction with other drugs and can therefore be used in conjunction with statins or other lipid-lowering drugs. Coadministration of cholestyramine decreases its bioavailability, while the concomitant use of gemfibrozil and fenofibrate slightly increases its availability. This agent can reduce cyclosporine levels.[47]

MATERIALS AND METHOD OF STUDY

The study of lipid profile in patients of chronic kidney disease was undertaken in The Department of Nephrology, Madurai medical college, Madurai.

SUBJECTS FOR THE STUDY

- The study group constituted patients of
    a) Chronic kidney disease on conservative management
    b) Chronic kidney disease on regular hemodialysis.
    c) Post Renal Transplantation with normal renal function.
- The control group constituted twenty healthy adults – 10 males and 10 females of different age groups whose ages compared well with that of study group.

SELECTION OF CASES

STUDY GROUP

a. Patients with chronic kidney disease on conservative management for a period of at least 6 months comprising of 10 males and 10 females within the age group of 20-50 years with none of them having diabetes were taken up.

b. Patients presenting with end stage renal failure on maintenance hemodialysis for period of 3 months comprising of 11 males and 9

females, all falling within the age group of 20 years to 50 years were taken up and none of them had Diabetes .

c. Post transplant patients with normal renal functions comprising of 10 males and 10 females within the age group of 20- 50 years and none of them had Diabetes.

CONTROL GROUP

This group consisted of 10 males and 10 females whose age group compared well with that of the study group. It was ascertained that none of them had hypertension, diabetes mellitus, renal or liver disease or any other metabolic disorder.

METHOD OF STUDY

Estimation of lipid profile

The various parameters analysed were :

- Serum total cholesterol (TC)
- Serum high density lipoprotein cholesterol (HDL)
- Serum low density lipoprotein cholesterol (LDL)
- Serum triglycerides (TG)
- Ratio of serum total cholesterol to high density lipoprotein cholesterol (TC/HDL).

Samples were collected after a 12 hour fast to avoid post prandial rise in serum triglyceride level.

Analysis of total cholesterol, triglycerides and HDL was done by use of an autoanalyser. Serum LDL cholesterol was calculated by Frederickson Friedwald's formula according to which LDL=total cholesterol – (HDL+VLDL). VLDL was calculated as 1/5th of triglycerides. LDL= Total Cholesterol –(HDL+ (triglycerides / 5), in mg/dL. The results were statistically analysed.(one way ANOVA, 't' test)

RESULTS

Table – 1

Values of Total cholesterol in different groups

Total cholesterol mg/dl	Conservative N=20	Post Transplant N=20	Haemodialysis N=20	Control N=20
< 200	20	14	18	20
200 - 239	0	6	2	0
> 240	0	0	0	0

Table – 2

Values of Triglycerides in different groups

Triglycerides mg/dl	Conservative N=20	Post Transplant N=20	Haemodialysis N=20	Control N=20
< 150	11	0	1	19
150 - 199	9	8	19	1
> 200	0	12	0	0

Table – 3

Values of HDL in different groups

HDL mg/dl	Conservative N=20	Post Transplant N=20	Haemodialysis N=20	Control N=20
< 40	18	13	17	0
40 - 59	2	7	3	20
> 60	0	0	0	0

Table – 4

Values of LDL in different groups

LDL mg/dl	Conservative N=20	Post Transplant N=20	Haemodialysis N=20	Control N=20
< 100	18	6	18	20
100 - 129	2	11	2	0
> 130	0	3	0	0

Table – 5

Values of total cholesterol / HDL ratio in different groups

Total cholesterol/HDL	Conservative N=20	Post Transplant N=20	Haemodialysis N=20	Control N=20
<4	2	0	6	20
4 - 6	18	18	14	0
> 6	0	2	0	0

Table – 6

Serum Total cholesterol in Different groups with their comparison

Group	No.of cases	Mean	P value	Significance
Conservative	20	158.45	< 0.001	Significant
Post transplant	20	190.15	< 0.001	Significant
Haemodialysis	20	147.3	< 0.001	Significant
Control	20	126.6		

Table 6 shows that the mean total cholesterol of the post transplant group is significantly high compared to other groups.

TOTAL CHOLESTEROL

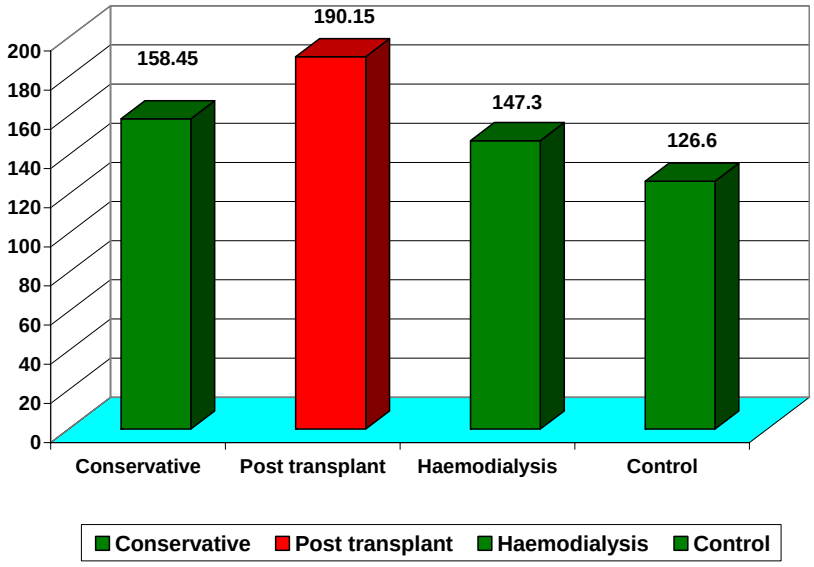


Table – 7

Serum triglyceride in Different groups with their comparison

Group	No.of cases	Mean	P value	Significance
Conservative	20	153.55	< 0.001	Significant
Post transplant	20	208.25	< 0.001	Significant
Haemodialysis	20	161.8	< 0.001	Significant
Control	20	120.25		

Table 7 shows that the serum triglyceride levels is significantly high in all the groups when compared with control group.

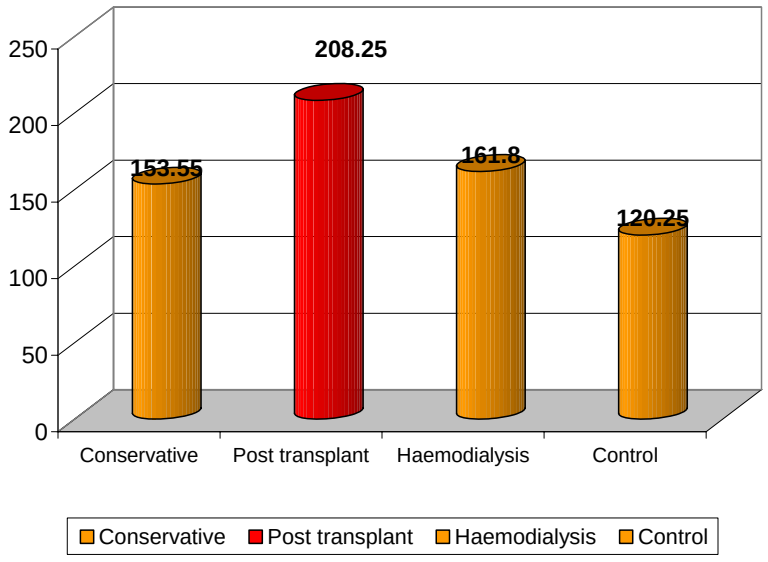
Table – 8

Serum LDL in Different groups with their comparison

Group	No.of cases	Mean	P value	Significance
Conservative	20	92.35	< 0.001	Significant
Post transplant	20	110.95	< 0.001	Significant
Haemodialysis	20	78.8	< 0.001	Significant
Control	20	58.9		

Table 8 shows that the mean LDL cholesterol of the post transplant significantly high in comparison with the other groups.

TRIGLYCERIDES



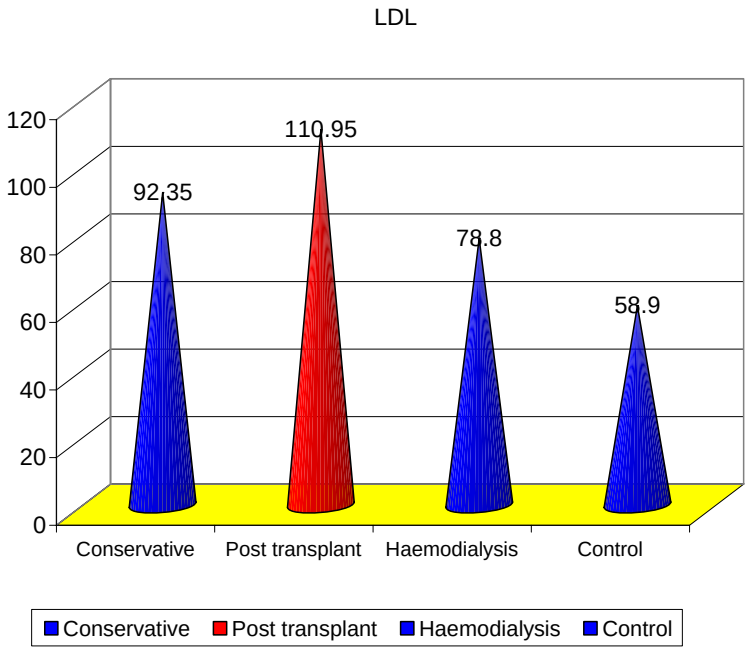

LDL
120
100
80
60
40
20
0
92.35
110.95
78.8
58.9
Conservative
Post transplant
Haemodialysis
Control
Conservative
Post transplant
Haemodialysis
Control

Table – 9

Serum HDL in Different groups with their comparison

Group	No.of cases	Mean	P value	Significance
Conservative	20	36.3	< 0.001	Significant
Post transplant	20	37.9	< 0.001	Significant
Haemodialysis	20	36.15	< 0.001	Significant
Control	20	43.7		

Table 9 shows the mean HDL cholesterol is significantly low in all the three gropus.

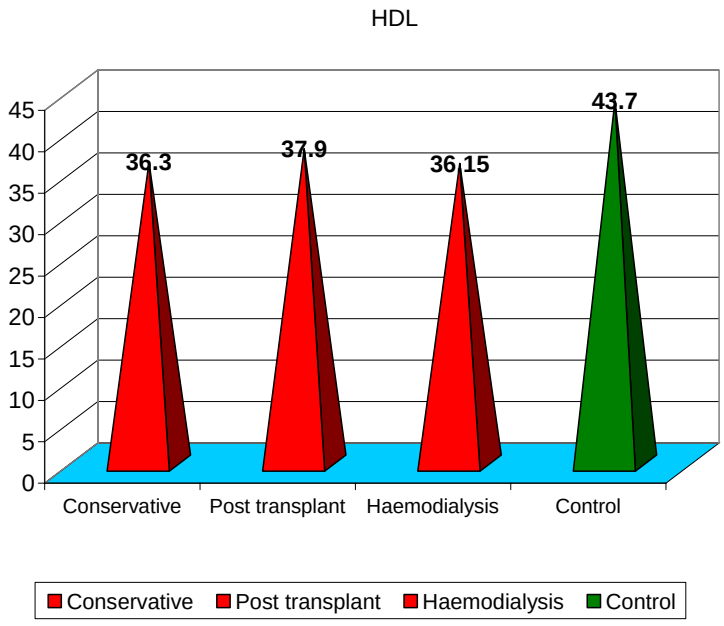
Table – 10

Total cholesterol / HDL ratio

in Different groups with their comparison

Group	No.of cases	Mean	P value	Significance
Conservative	20	4.3	< 0.001	Significant
Post transplant	20	5.02	< 0.001	Significant
Haemodialysis	20	3.9	< 0.001	Significant
Control	20	2.9		

Table 10 shows the ratio of total cholesterol /HDL in post transplant group is significantly high when compared to other groups.


HDL
45
40
35
30
25
20
15
10
5
0
36.3
37.9
36.15
43.7
Conservative
Post transplant
Haemodialysis
Control
Conservative
Post transplant
Haemodialysis
Control

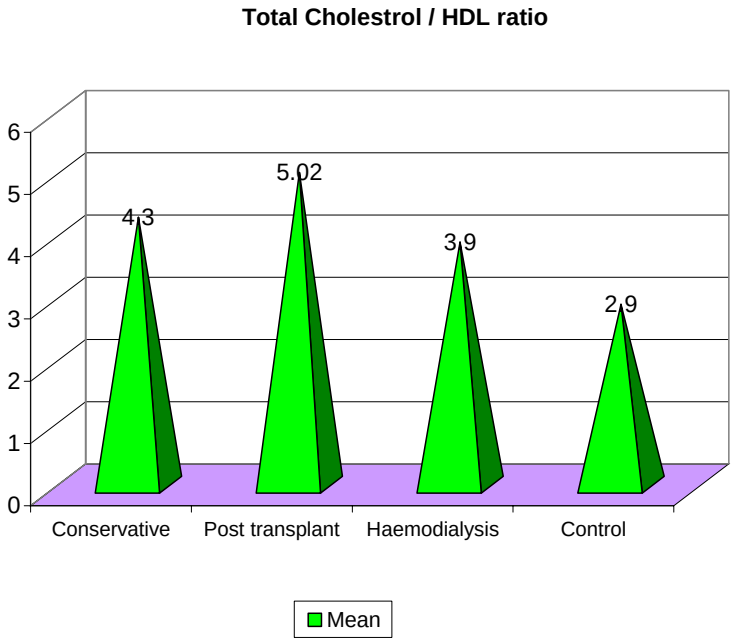

Total Cholestrol / HDL ratio
6
5
4
3
2
1
0
4.3
5.02
3.9
2.9
Conservative
Post transplant
Haemodialysis
Control
Mean

Table – 11

Conservative group

Conservative	Male	Female	P value	Significance
TCL	160	156	0.205	Not Significant
TGL	163	144	<0.001	Significant
HDL	36	36	0.654	Not Significant
LDL	92	92	0.918	Not Significant
Tchl/HDL	4.4	4.3	0.308	Not Significant

Table 11 shows except for triglycerides there is no significant difference noticed on comparison of lipid profile values between male and female in conservative groups.

Table – 12

Post transplant group

Post transplant	Male	Female	P value	Significance
TCL	186	193	0.457	Not Significant
TGL	210	206	0.836	Not Significant
HDL	37.9	37.9	0.968	Not Significant
LDL	106.9	115	0.335	Not Significant
Tchl/HDL	4.9	5.1	0.477	Not Significant

Table 12 shows comparison of lipid profile between male and females in post transplant group showed no significant difference.

Table – 13

Haemodialysis group

Haemodialysis	Male	Female	P value	Significance
TCL	142	142	0.912	Not Significant
TGL	157	162	0.762	Not Significant
HDL	36	36.3	0.938	Not Significant
LDL	75	73.4	0.779	Not Significant
Tchl/HDL	3.9	3.9	0.797	Not Significant

Table 13 shows no significant difference in lipid profile values noticed between male and females in hemodialysis group.

Table – 14

Control group

Control	Male	Female	P value	Significance
TCL	125	127.7	0.586	Not Significant
TGL	114.8	125.7	0.081	Not Significant
HDL	44.2	43.4	0.456	Not Significant
LDL	58.9	58.9	1.00	Not Significant
Tchl/HDL	2.8	2.9	0.314	Not Significant

SUMMARY OF THE OBSERVATION

The lipid profile study of chronic kidney disease patients on conservative management, on regular haemodialysis and post transplantation showed the following changes.

1. SERUM TOTAL CHOLESTEROL

The total cholesterol levels were normal in all the 20 (100%) patients in the conservative management group. The levels were normal in 18(90%) and borderline high in 2(10%) in the haemodialysis (CKD – HD) group . In the post transplant group the levels were normal in 14(70%) and borderline high in 6(30%) patients.

The mean total cholesterol in the control group was 126.60mg/dl, the conservative management group was 158.45mg/dl, CKD – HD group was 147.3mg/dl and the post transplant group was 190.15mg/dl. The mean cholesterol was significantly increased in the post transplant group when compared to the other groups.

2. SERUM TRIGLYCERIDES

The triglycerides levels were normal in 11 (55%) and borderline high in 9(45%) patients in conservative management group.

The levels were normal in 1(5%) and borderline high in 19(95%) patients in the CKD – HD group. In the post transplant group the levels were borderline high in 8(40%) and elevated in 12(60%) patients.

The mean triglyceride of the control group was 120.25mg/dl, the conservative management group was 153.55mg/dl, CKD – HD group was 161.80mg/dl and the post transplant group was 208.25mg/dl. The mean triglycerides level was significantly increased in all study groups when compared to controls.

3. LDL CHOLESTEROL

The LDL cholesterol levels were normal in 18(90%) and borderline high in 2(10%) patients in the conservative management group.

The LDL cholesterol levels were normal (below 100 mg/dl) in 18(90%) and borderline high in 2(10%) patients in the CKD – HD group. In the post transplant group the levels were normal in 6(30%), borderline high in 11(55%) and elevated in 3(15%) patients.

The mean LDL cholesterol of the control group was 58.90mg/dl, the conservative management was 92.35mg/dl, the CKD – HD group was 78.8mg/dl and the post transplant group was 110.95mg/dl. The mean LDL cholesterol was significantly increased in all study groups when compared to controls, whereas in conservative group and haemodialysis group the mean LDL cholesterol was within optimal level (<100mg/dl).

4. HDL CHOLESTEROL

The HDL cholesterol levels were decreased in 18 (90%) and normal in 2(10%) patients in the conservative management group. The levels were

decreased in 17(85%), normal in 3 (15%) patients in CKD – HD group. In the post transplant group the levels were decreased in 13(65%) and normal in 7(35%) patients. The mean HDL cholesterol of the control group was 43.7mg/dl, conservative management group was 36.3mg/dl, CKD – HD group was 36.15mg/dl and the post transplant group was 37.9mg/dl. HDL cholesterol was significantly decreased in all study groups when compared to controls.

5. RATIO OF TOTAL CHOLESTEROL/HDL CHOLESTEROL

The total cholesterol/HDL ratio were normal in 2 (10%) and borderline high in 18(90%) patients in conservative management group. The levels were normal in 6 (30%) and borderline high in 14(70%) patients in the CKD – HD group . In the post transplant group the levels were borderline high in 18(90%) and elevated in 2(10%) patients. The total cholesterol/HDL ratio of control group was 2.9, conservative management group was 4.3, CKD – HD group was 3.9 and the post transplant group was 5.02. The TC / HDL ratio was significantly increased in all study groups when compared to controls.

DISCUSSION

Chronic kidney disease (CKD) results in profound lipid disorders, which stem largely from dysregulation of high density lipoproteins (HDL) and triglyceride-rich lipoprotein metabolism. Specifically, maturation of HDL is impaired and its composition is altered in CKD. In addition, clearance of triglyceride-rich lipoproteins and their atherogenic remnants is impaired, their composition is altered, and their plasma concentrations are elevated in CKD. Impaired maturation of HDL in CKD is primarily due to down regulation of lecithin-cholesterol-acyltransferase and, to a lesser extent, increased plasma cholesteryl ester transfer protein (CETP). Triglyceride enrichment of HDL in CKD is primarily due to hepatic lipase deficiency and elevated CETP activity. The CKD induced hypertriglyceridemia, abnormal composition, and impaired clearance of triglyceride-rich lipoproteins and their remnants are primarily due to down regulation of lipoprotein lipase, hepatic lipase, and the very low density lipoprotein receptor, as well as, up regulation of hepatic acyl-CoA cholesterol acyltransferase (ACAT). In addition, impaired HDL metabolism contributes to the disturbance of triglyceride-rich lipoprotein metabolism. These abnormalities are compounded by down regulation of apolipoproteins apoA-I, apoA-II and apoC-II in CKD. Together, these abnormalities may contribute to the risk of atherosclerotic cardiovascular

disease and may adversely affect progression of renal disease and energy metabolism in CKD. This study was conducted to determine the lipid profile changes in chronic renal failure patients on conservative management, on regular hemodialysis and post renal transplant patients with normal renal function and to compare them with healthy controls.

The study population was 60 patients with 20 patients in each group and 20 healthy controls. Each group had 10 males and 10 females to compare the sex variation.

All the persons involved in the study were between 20-50 years. It was ensured that none of the control group had diabetes mellitus, hypertension, renal, liver or any metabolic disorder. It was also ensured that none of the patients in the study group had diabetes. Serum total cholesterol, HDL cholesterol, LDL cholesterol , Triglycerides, Total cholesterol /HDL cholesterol ratio were measured using an autoanalyser, after a 12 hour fast. The results were statistically analysed based on the following guidelines.

ADULT TREAMENT PANEL III (ATP III) GUIDELINES[50]

DYSLIPIDEMIA	LEVEL (mg /dl)
Total cholesterol	
Desirable	< 200
Borderline high	200-239
High	> 240
LDL cholesterol	
Optimal	< 100
Near optimal	100-129
Borderline	130-159
High	> 160
Triglycerides	
Normal	< 150
Borderline high	150 -199
High	200-499
Very high	> 500
HDL cholesterol	
Low	< 40

Lipid changes in CKD patient on conservative management : reported studies

1. The characteristic plasma lipid abnormality in CRF patients is moderate hypertriglyceridemia - this is due to impaired carbohydrate tolerance leading to increased hepatic synthesis of VLDL and decreased activity of lipoprotein lipase and hepatic triglyceride lipase leading to decreased fractional catabolic rate of triglycerides.
2. Decrease in HDL cholesterol level - this is due to the deficiency of LCAT which is essential for esterification of cholesterol. LCAT plays an important role in HDL mediated cholesterol uptake from the extra hepatic tissues and serves as a main determinant of HDL maturation and plasma HDL cholesterol level. Decrease in HDL level is also contributed by elevation of CETP.
3. Normal or slightly increased total cholesterol level.
4. Normal or slightly increased LDL cholesterol level.

Observation on lipid profile changes of CKD patients on conservative management showed the following results:

The mean age of the control group was 41.7 yrs and the conservative management group was 39.55 yrs**.** There was no significant difference in the lipid profile between the males and the females in the conservative

management group except for triglyceride level which showed significant difference. This may be due to different dietary pattern.

The total cholesterol levels were normal in all the patients in conservative group. The mean total cholesterol in the conservative management group was 158.45mg/dl and control was 126 mg/dl. This was statistically significant. The triglyceride levels were borderline high in 45%.The mean triglyceride level in the conservative management group was 153.55mg/dl and was significantly increased when compared to a mean of 126.6 mg/dl in the control group.

The LDL levels were normal in 90% and borderline high in 10% and HDL was <40mg/dl in 90%.The mean LDL cholesterol in the conservative management group was 92.35mg/dl and control was 58.9mg/dl. This difference was significant. The mean HDL cholesterol in conservative management group was 36.3mg/dl and was significantly decreased when compared to the controls. The mean TC/HDL cholesterol ratio in conservative management group was 4.31 and was significantly increased compared to control.

The final results revealed a (1) significant decrease in HDL cholesterol (2) significant increase in triglyceride levels (3) significant increase in TC/HDL cholesterol ratio (3) significant increase in serum total cholesterol and LDL cholesterol when compared to the control group.

The significant decrease in HDL could be due to various reasons mentioned earlier (decrease in LCAT, hepatic lipase activity, increase in ACAT, decrease in apoA-I and apoAII) and the cause for hypertriglyceridemia has been mentioned earlier.

In a study by Attman PO et al [51] revealed increased VLDL ; remnants and intermediate density lipoproteins; prolonged persistence of postprandial chylomicrons and accumulation of noncardioprotective acute phase HDL in renal disease patients. Another study by Bagdade, casaretto A, Albers J showed the same effects of chronic uremia on lipid profile.[52]

Lipid changes in post transplant patients – reported studies

The characteristic pattern noted in earlier studies were

(1) Increase in total cholesterol with increase in VLDL and LDL cholesterol

(2) Increase in Triglycerides.

(3) Decrease in HDL cholesterol

In posttransplant patients different lipid profile changes are due to the various effects of immunosuppressive drugs, such as calcineurin inhibitors (cyclosporine and tacrolimus), antiproliferative drugs (mycophenolate mofetil and azathioprine), mammalian target of rapamycin inhibitors (sirolimus and everolimus), and corticosteroids.

Observation on lipid profile changes of post transplant patients showed the following results

The mean age of this group was 38.2yrs and there was no significant difference in the lipid profile between males and females.

The total cholesterol levels were borderline high in 30% of the patients in this group. The mean total cholesterol in post transplant group was 190.15mg/dl and was significantly increased when compared to the controls which was 126mg/dl. The triglyceride levels were borderline high in 40% and elevated in 60%. The mean triglyceride level in the post transplant group was 208.25mg/dl and was significantly increased when compared to 120.25mg/dl in the controls.

The LDL levels were borderline high in 55% and elevated in 15% and HDL was decreased in 65% of the cases. The mean LDL cholesterol in the post transplant group was 110.95mg/dl and was significantly increased when compared to 59mg/dl in the controls. The mean HDL cholesterol in the post transplant group was 37.9mg/dl and was significantly decreased when compared to the control group which was 43.7mg/dl. The mean TC/HDL cholesterol ratio in the post transplant group was 5.02 and was significantly increased when compared to 2.9 in the controls.

The final results revealed a (1) significant increase in serum triglycerides (2) significant increase in total cholesterol (3) significant

increase in LDL cholesterol (4) significant decrease in HDL cholesterol (5) significant increase in total cholesterol/HDL ratio when compared to the control group.

In a study done by Ziad A.Massy, B.L. Kasiske [55] reported same changes of serum lipids include increases in both triglycerides and total cholesterol. Another study by Ponticelli C,Barbi GL ,Cantaluppi A et al [35]revealed the same lipid disorders in renal transplant recipients. Study done by Brown et al revealed that 83-87 % of post transplant patients had high total cholesterol,90% had high LDL which correlates with our study.

Lipid changes in CKD patients on Haemodialysis : Reported studies

1. Moderate increase in triglyceride levels
2. Decrease in HDL levels
3. Normal / slightly elevated total cholesterol, LDL cholesterol
4. Increased Lp(a)
5. Increased apoB and apoA-IV and decreased apo A-I

In addition to factors responsible for renal dyslipoproteinemia the other contributing factors in a CKD-HD patient are

1. Reduced lipolytic activity following repeated heparinisation. The exact reason is not understood but may be due to functional insulin deficiency or insulin resistance, and also due to the presence of non dialyzable factor of lipolytic enzyme (lipoprotein lipase), in the

plasma of CKD-HD patients. The changes are more pronounced with the use of conventional heparin than low molecular weight heparin.

2. The presence of Acetate in the dialysate which gets converted to long chain fatty acids and later to cholesterol in the liver.

3. Carnitine deficiency results in impaired fatty acid oxidation.

Observation on lipid profile changes of CKD- HD showed the following results

The mean age of the hemodialysis group was 38.95 yrs. There was no significant difference in the lipid profile between males and females in this group.

The total cholesterol levels were normal in 90% and elevated in 10% of cases. The mean total cholesterol in the CKD – HD group was 147.3mg/dl and control was 126mg/dl. This difference was significant. The triglyceride levels were normal in 5% and borderline high in 95%. The mean triglyceride level in the CKD – HD group was 161.8 and was significantly increased when compared to the controls.

The LDL cholesterol levels were normal in all of patients in this group. The mean LDL cholesterol in the CKD – HD group was 78.8mg/dl and in the control was 58.9mg/dl. This difference was significant. The HDL cholesterol levels were below 40 mg/dl in 85%.The mean HDL cholesterol

in the CKD – HD group was 36.15mg/dl and was significantly decreased when compared to 43.7mg/dl in the control group. The Total Cholesterol / HDL ratio was elevated in 12 (60%) patient. The mean Total Cholesterol/HDL cholesterol ratio in CKD – HD group was 3.9 and was significantly increased when compared to 2.9 in the control group.

The final results revealed a

(1) significant decrease in HDL cholesterol

(2) significant increase in triglyceride levels

(3) significant increase in TC/HDLcholesterol ratio

(4) significant changes in serum total cholesterol and LDL

In a study by Deighan CJ, Caslake MJ, McConnel revealed tha same lipid changes in dialysis patients. Shoji T , and Huttunnen JK tested the role of heparin in the pathogenesis of HD induced dyslipidemia revealed the same changes[53,54]. But According to ATP III guidlines 55.7% would require treatment based on LDL >100.

From this study it is inferred that dyslipidemias are common in chronic renal failure patients and especially more pronounced in transplant recipients.

The National Kidney Foundation task force on CVD (Cardiovascular disease) concluded that the incidence of ACVD is higher in patients with CKD compared to the general population. The task force concluded that

patients with CKD should be considered to be in the highest risk category, ie,a CHD (Coronary heart disease) risk equivalent, for risk factor management. The principal reason to evaluate dyslipidemias in patients with CKD is to detect abnormalities that may be treated to reduce the incidence of ACVD (Atherosclerotic Cardiovascular Disease). The appropriate management of dyslipidemia plays an important role in the overall care of the patient with chronic and ESRD and renal transplantation. Evaluation of dyslipidemias should occur at presentation with chronic renal disease, following a change in treatment modality and annually. The American Society of Transplantation recommend tha a lipid profile should be measured during the first 6 months post transplant, at 1 year after transplant and annually thereafter. Appropiate therapeutic life style change and drug therapy should be started. LDL level should be maintained below 100mg/dl, Triglycerides below 150 mg/dl and HDL should be above 40. Drug therapy should be used for LDL levels of 130 mg/dl and also for LDL levels of 100-129 mg/dl after 3 month of therapeutic life style change.

CONCLUSION

- There is no significant difference in the lipid profile between males and females in the different groups except for triglyceride level in conservative group.
- The mean total cholesterol is significantly increased in chronic kidney disease patients on conservative group, on haemodialysis group and post transplant group when compared to controls ($p<0.001$). Among the three groups total cholesterol is significantly increased in post transplant group.
- The mean triglyceride level is significantly increased in CKD patients on conservative management ($p<0.001$), on haemodialysis ($p<0.001$) and after transplantation ($p<0.001$). According to ATP III guidelines the mean triglycerides is high (> 200mg/dl) in post transplant group and border line high (150-199) in the conservative and haemodialysis group.
- The mean LDL cholesterol is significantly increased in the post transplantation group, on haemodialyis group and conservative group. As per ATP III guidelines the mean LDL cholesterol is high (> 100mg/dl) in the post transplant group.

- The mean HDL cholesterol is significantly decreased in the conservative management group ($p<0.001$), the hemodialysis group ($p<0.001$) and in the post transplant group ($p<0.001$).
- The total cholesterol to HDL cholesterol ratio is significantly increased in CKD patients on conservative management ($p<0.001$), on haemodialysis ($p<0.001$) and after transplantation ($p<0.001$). Among the three groups the ratio is significantly increased in post transplant group.

Dyslipidemia is a very common complication of CKD. Disturbance in lipoprotein metabolism usually follow a downhill course that parallels the deterioration in renal function.The lipoprotein abnormalities caused by renal insufficiency also may further influence the progression of renal failure. Since dyslipidemia and its complications are more prevalent in chronic kidney disease patients, early diagnosis of dyslipidemia is indicated and potential therapeutic approaches (therapeutic life style changes and pharmacotherapy) should be initiated to limit the long term consequences of cardiovascular disease in this population of patients, whose longevity is anticipated to increase with dialysis and transplantation.

LIMITATIONS OF THE STUDY

1. Sample size in our study is relatively small.
2. Staging of CKD and dyslipidemia are not correlated in this study.

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PROFORMA

NAME :

AGE :

SEX :

HISTORY OF DIABETES - PRESENT / ABSENT

HISTORY OF HYPERTENSION - PRESENT / ABSENT

CHRONIC KIDNEY DISEASE

DURATION:

TREATMENT:

1. CONSERVATIVE
2. HAEMODIALYSIS
3. RENAL TRANSPLANTATION

LABORATORY INVESTIGATIONS:

1. BLOOD UREA:
2. SERUM CREATININE:
3. FASTING LIPID PROFILE:
4. TOTAL CHOLESTEROL /HDL RATIO:

ABBREVIATIONS

CKD	-	Chronic Kidney Disease
ESRD	-	End stage renal disease
TG	-	Triglyceride
TC	-	Total cholesterol
HDL	-	High density lipoprotein
LDL	-	Low density lipoprotein
VLDL	-	Very low density lipoprotein
HD	-	Hemodialysis
LPL	-	Lipoprotein lipase
LCAT	-	Lecithin cholesterol acyl transferase
ACAT	-	acyl-CoA cholesterol acyltransferase
CETP	-	Cholesteryl ester transfer protein
ACVD	-	Atherosclerotic Cardiovascular Disease

MASTER CHART

CKD CONSERVATIVE MANAGEMENT

S.No.	Name	Sex	Age	TChl	TGL	HDL	LDL	TChl/HDL
1	Arumugam	M	41	172.00	180.00	36.00	100.00	4.8
2	Ramu	M	40	164.00	175.00	37.00	92.00	4.4
3	Mookan	M	39	163.00	160.00	38.00	93.00	4.3
4	Thangaraj	M	40	166.00	180.00	35.00	95.00	4.7
5	Alagarsamy	M	40	162.00	170.00	34.00	94.00	4.8
6	Ganesan	M	41	156.00	160.00	36.00	90.00	4.3
7	Muniasamy	M	39	148.00	158.00	35.00	81.00	4.2
8	Ponnaiah	M	42	158.00	146.00	36.00	94.00	4.4
9	Thangam	M	38	162.00	146.00	37.00	97.00	4.4
10	Ravikumar	M	48	154.00	156.00	37.00	89.00	4.2
11	petchiammal	F	42	160.00	148.00	35.00	97.00	4.6
12	muthal	F	45	150.00	140.00	36.00	87.00	4.2
13	karupaiye	F	36	148.00	140.00	34.00	84.00	4.4
14	lakshmi	F	47	160.00	142.00	36.00	98.00	4.4
15	muniammal	F	43	164.00	146.00	35.00	99.00	4.7
16	rakkammal	F	35	166.00	146.00	36.00	102.00	4.6
17	thenmozhi	F	48	156.00	142.00	40.00	92.00	3.9
18	vasantha	F	39	146.00	138.00	42.00	79.00	3.5
19	meena	F	46	162.00	150.00	36.00	96.00	4.5
20	princemarry	F	46	152.00	148.00	35.00	88.00	4.3

Post Transplant

S.No.	Name	Sex	Age	TChl	TGL	HDL	LDL	TChl/HDL
1	Saleem	M	37	200	332	40	94	5.0
2	Saktheswaran	M	32	180	231	40	94	4.5
3	Ellareddy	M	42	167	185	36	94	4.6
4	Saravanan	M	40	174	150	39	105	4.5
5	Guruchandran	M	38	172	166	37	103	4.6
6	Nataraj	M	39	202	240	40	114	5.1
7	Prabhakaran	M	45	187	208	35	110	5.3
8	Suresh	M	30	190	254	40	99	4.8
9	Raman	M	29	228	170	37	157	6.2
10	Bharathi	M	37	168	167	35	99	4.8
11	jameela	F	41	189	226	37	107	5.1
12	jeeva	F	35	209	228	40	123	5.2
13	kala	F	40	174	169	35	112	5.0
14	ramya	F	42	180	200	40	100	4.5
15	Ramani	F	38	177	166	39	105	4.5
16	Ambiga	F	42	196	208	37	117	5.3
17	Chandra	F	36	179	226	37	97	4.8
18	Tamilselvi	F	42	179	185	40	102	4.5
19	Parvathi	F	38	232	204	37	154	6.3
20	Suganya	F	41	220	250	37	133	5.9

CKD Hemodialysis

S.No.	Name	Sex	Age	TChl	TGL	HDL	LDL	TChl/HDL
1	Thothan	M	45	140	158	42	69	3.3
2	Murugan	M	35	203	190	37	128	5.5
3	Palani	M	41	138	154	36	72	3.8
4	Rajan	M	42	136	150	37	69	3.7
5	Kanan	M	38	135	148	34	72	4.0
6	Balamurugan	M	41	140	156	38	71	3.7
7	Kuppaiah	M	46	142	155	33	78	4.3
8	Elango	M	39	148	170	34	80	4.4
9	Karthikpandi	M	41	146	162	35	78	4.2
10	Manikandan	M	37	150	168	36	82	4.2
11	Rani	F	38	144	166	41	70	3.5
12	Paalaniyammal	F	42	140	163	34	74	4.1
13	Jansi	F	40	136	170	35	67	3.9
14	Shanthi	F	41	135	168	33	69	4.1
15	Priya	F	37	142	163	34	76	4.2
16	Rajammal	F	42	146	164	36	77	4.1
17	Jeena	F	38	201	172	42	125	4.8
18	Lurthubegam	F	28	136	156	34	71	4.0
19	Lakshmirani	F	32	138	154	38	70	3.6
20	Durga	F	36	150	149	36	78	4.2

CONTROL GROUP								
S.No.	**Name**	**Sex**	**Age**	**TChl**	**TGL**	**HDL**	**LDL**	**TChl/HDL**
1	Abubakar	M	40	152	128	42	84	3.6
2	Murugapandi	M	27	115	100	45	50	2.6
3	Venkatesh	M	42	127	100	43	64	3.0
4	Ganesan	M	45	112	120	40	48	2.8
5	Arumugam	M	40	124	100	46	58	2.7
6	Arokiadass	M	38	132	112	48	68	2.8
7	Ibraheem	M	42	126	110	42	62	3.0
8	Raman	M	46	119	120	44	51	2.7
9	Muthupandi	M	39	120	128	42	52	2.9
10	Karthikeyan	M	39	128	130	50	52	2.6
11	manimegalai	F	42	128	151	42	56	3.0
12	Pavithra	F	47	131	136	44	60	3.0
13	Alamelu	F	42	138	142	48	62	2.9
14	Mookammal	F	38	129	126	40	64	3.2
15	Muthupechi	F	39	120	132	42	51	2.9
16	Renuga	F	29	132	117	43	62	3.1
17	Vadivu	F	42	128	118	45	59	2.8
18	Ratha	F	40	126	116	47	56	2.7
19	Punitha	F	38	118	107	40	56	3.0
20	Amutha	F	36	127	112	41	63	3.1